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(54) ECTOPARASITICIDAL TOXICANTS

(71) We, STAFFORD-MILLER LIMITED, of 166 Great North Road, Hatfield, Hertfordshire, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described, in and by the following statement:-

This invention relates to ectoparasiticidal toxicants and to methods of controlling ectoparasites, other biting insects and mites.

More particularly, the invention relates to the use of certain insect toxicants for treatment of human beings and other substrates infested with lice, mites, and/or their ova. Certain of the ectoparasiticidal toxicant components now employed serve additionally to control pain or itch related to infestation, and can be used in adjunctive therapy to relieve pain or itch. Certain other toxicant components exhibit other adjunctive activity.

Many species of insects encase their ova in protective sheaths which are impregnable to most toxicants. The "gestation" period of the egg is often relatively long in comparison to the life cycle of the adult forms. Thus, an agent effective only against adults must persist for the lifetime of the developing ovum or must be reapplied as successive hatching occurs. The ideal drug for treatment of ectoparasites should be active against the ova as well as the adult and nymphal forms, and should be relatively non-toxic to the host.

In contrast to drugs used by inuction, compositions designed to be used as shampoos or body washes must fulfil certain criteria. For example, they must either exert their parasiticidal and ovicidal effects within a very short time, or must resist washing off during the course of ablutions.

There are only a relatively few ectoparasiticides which are commercially available today. The most popular pediculicidal toxicants are Lindane (gamma benzene hexachloride), Malathion [(S-1,2-dicarbethoxyethyl)-0,0-dimethyl phosphorodithioate], synergized pyrethrins and Cuprex (a combination of tetrahydronapthalene, copper oleate and acetone, the acetone not asserted to be active). Sulphur, Lindane, benzyl and crotamiton are the best known agents for scabies. Because of increased concern about the overall safety of some of the known ectoparasitic toxicants, the search for new, safe and effective ectoparasiticides has intensified recently.

Ectoparasites such as lice and mites cause pruritus or pain in their animal or human hosts. Therapy which simply kills the parasite leaves the host with subcutaneous or intradermal residues which continue to itch for significant time periods after the infestation is extinguished. Furthermore, scratching during and after the episode frequently leads to painful excoriation. Drugs presently used in treatment of human or animal ectoparasitic infestations are either dermal irritants or contain as active ingredients components having at least a potential liability for neurotoxic side effects to the host.

It is the objection of this invention to provide safe and effective toxicants for use against insects and their ova.

According to the present invention there is provided a method of controlling ectoparasites or their ova which comprises applying to a substrate a mixture of (a) a

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monohydric alcohol whose logarithm of the partition coefficient between N-octanol and water (log P) is at least 0.61; and (b) a polyoxyethylene derivative having an HLB of 2.5 – 13.5 and being an alkyl ether, aralkyl ether, alkyl ester or block polymer of polyoxyethylene preferably with (c) an N-fatty-β-aminopropionic acid preferably at pH less than 7 and/or (d) an N-C_{12-24} acyl-N-methyl glycine preferably at pH less than 5.5.

For use in the method the invention also provides an insecticidal, typically ectoparasiticidal or ovicidal, toxicant composition comprising an active toxicant mixture which includes the components (a) and (b) above, preferably in admixture with (c) and/or (d), together with an inert pharmaceutically acceptable carrier.

The active toxicant composition can be in the form of a liquid, powder, lotion, cream, gel or aerosol spray, or foam as the result of formulation with inert pharmaceutically acceptable carriers by procedures well known in the art. Any pharmaceutically acceptable carrier, whether aqueous or not aqueous, which is inert to the active ingredient can be employed. By inert is meant that the carrier does not have a substantial detrimental effect on the pediculicidal or ovicidal toxicant activity of the active ingredient. The carrier may also be additive or synergistic to the primary active ingredient.

The amounts and relative proportions of the components (a) and (b), and (c) and/or (d) when present, are not critical. The formulation can be varied as desired depending upon the particular insecticidal characteristics which are sought.

The active components are preferably incorporated into the toxicant composition used to treat the substrate (human or animal, in need of such treatment, believed to be in need of such treatment, or desired to be prophylactically protected) such that considered as the total composition they are present in an "effective toxicant amount". By such amount is meant the amount which will cause at least 50% of the lice and ova exposed respectively in the pediculicide and ovicide tests described herein to die within 24 hours in the case of lice and within 2 weeks in case of ova. A preferred effective toxicant amount gives a mortality of at least 75%. Preferably both the components (a) and (b) are present in their respective effective toxicant amounts, and when present it is preferred that components (c) and (d) are used in an amount which increases the mortality rate in the tests by at least 20%.

Each of the defined class of components (a) to (d) is described in more detail below. For convenience, the discussion of each class is developed separately, but it is necessary to bear in mind that one is using a combination of compounds from different classes. In the separate descriptions we give results of the tests for determining effective toxicant amounts of typical examples for the components (a) to (d), though it is necessary to bear in mind the possibility of synergism when predicting the activity of the total compositions.

Instead of considering the preferred compositions in terms of effective toxicant amounts, it is possible to give preferred concentrations for the components in the compositions of the invention. As is discussed below for each component there is no direct correlation between concentration and effective toxicant amount, and as such there is no direct correlation between the following preferred compositions and those which are preferred by virtue of the fact that they contain an effective toxicant amount of the toxicants.

Component	*Preferred (%)**	*More Preferred (%)*
(a)	5 to 40	10 to 20
(b)	1 to 40	1 to 20
(c)	0 to 20	0 to 10
(d)	0 to 20	0 to 10

*The concentrations are selected within the ranges given so as to total less than 100%.

The pediculicidal, ovicidal and miticidal tests referred to are carried out as follows:

Pediculicidal activity: A 50 ml beaker is filled with tap water and allowed to come to room temperature (about 24°C). Ten young adult male and ten young adult female lice *(Pediculus humanus corporis)* of the same age group and from the same stock colony are placed by a 2x2 cm coarse mesh patch. The sample to be tested, maintained at room temperature, is shaken until homogeneous and placed into a 50 ml beaker. The mesh patch is placed into the sample immediately after pouring, allowed to submerge, and after two minutes is removed and immediately plunged into the beaker containing the tap water. The patch is vigorously agitated every ten seconds and after one minute the patch is removed and placed on paper toweling. The lice are then transferred to a 4x4 cm black corduroy cloth patch and this point of time is considered zero hours. Thereafter, the corduroy patch is placed in a petri dish which is covered and stored in a 30°C holding chamber. 24 hours

later the numbers of live and dead lice are determined.

Ovicidal activity: 15 adult, 5 to 10 day old, female lice *(Pediculus humanus corporis)* are placed on a 2x2 cm nylon mesh patch which is placed in a petri dish, covered and maintained in an incubator at 30°C for 24 hours. The adult lice are then removed and the number of plump, viable eggs and shriveled non-fertile eggs on the patch are recorded. The sample to be tested, maintained at room temperature, is shaken until homogeneous and poured into a 50 ml beaker. Immediately after the pouring, the mesh patch is placed into the beaker, allowed to submerge, and after two minutes is removed and immediately plunged into a 50 ml beaker containing tap water at room temperature (about 24°C). The patch is vigorously agitated every ten seconds and after one minute, the patch is removed and placed on paper towelling for one minute. The patch is then placed in a petri dish which is covered and stored in the 30°C incubator. Fourteen days following treatment, the number of hatched eggs and the number of shriveled or unhatched eggs is noted.

In both the pediculicidal and ovicidal two minute immersion tests, controls are run in identical manners to that described with room temperature (24°C) tap water substituted for the sample to be tested. The results of the tests reported are net results.

Miticidal activity. Into a one cubic foot chamber, held at room temperature, is placed a covered microscope depression slide containing ten adult mixed sex mites, *Psoroptis equivar. caniculi.* The slide is positioned at a distance of ten inches horizontally and four inches below the activator of a mechanical spray device and uncovered. The mechanical pump spray device delivers 50 micrograms of sample per depression of the activator. The sample to be tested, maintained at room temperature, is shaken until homogeneous and placed in the mechanical pump spray device. The primed activator is depressed twice, releasing 100 micrograms of spray mist into the closed chamber. The mist is allowed to settle and the slide containing the mites is removed and covered. This point of time is considered zero hours. The covered slide is then held at room temperature for 24 hours. Miscroscopic observations are noted at 0, 1, 3, and 24 hours post treatment. Controls are run in an identical manner as that described using water or the diluting agent, and net mortality results are reported.

Component (a) The toxicant components (a) of the instant invention are those higher alcohols which have a logarithm of their partition coefficient between n-octanol and water of at least 0.61. In themselves they exhibit pediculicidal and/or ovicidal activity, and reference is made to our application No. 32139/77 (Serial No. 1604857) which is concerned with this finding. The alcohols are known materials and have been incorporated into many pharmaceutical and cosmetic preparations. For example, cetyl alcohol constitutes 15% of a published hair groom gel and 61% of a floating bath oil, and lauryl or isocetyl or dodecyl alcohol about 30% of a mineral oil gel. Cetyl alcohol and lauryl alcohol are also listed under the United States Food & Drug Administration's approved Synthetic Flavour Substituents and Adjuvants list (21 CFR 1.1.1164). Cetyl alcohol has been used in compositions applied to the skin (U.S. 3,226,295 and 3,943,234) and lauryl alcohol derivatives have been used in parasiticides (U.S. 2,030,093).

The toxicants (a) of the instant invention are monohydric alcohols, ROH, in which R is a substituted or unsubstituted alkyl group. The substituting moieties can include aryl, aryloxy halogen. The R groups generally contain at least 4 carbon atoms and the maximum number of carbon atoms is not restricted but is generally 24 or less. It has been found that in order that the alcohols contribute satisfactory pediculicidal and/or ovicidal activity, the logarithm of the partition coefficient (hereinafter log P) for the compound between n-octanol and water must be at least 0.61. Log P values can be obtained by consulting Leo et al, *Chemical Review, 71*, 525 (1971) or calculated by the method therein described. When pediculicidal activity is desired, it is preferred that the alcohols be unsubstituted alkyl alcohols having log P values of 1.16-7.13. When ovicidal activity is desired, it is preferred that the alcohols have log P values of 1.1-7.13 and preferably are alkyl alcohols having log P values of 2.3-5.13. Accordingly, when a contribution by component (a) of both pediculicidal and ovicidal activity is desired, it is preferred to employ an unsubstituted alkyl alcohol having log P values of 2.13-5.1.

Typical of the monohydric alcohols which can be employed in this invention are n-butanol, sec-butanol, iso-butanol (but not tert-butanol), iso-pentanol, n-pentanol, n-hexanol, n-octanol, n-decanol, n-dodecanol, hexadecyl alcohol, oleyl alcohol, benzyl alcohol, 2-phenoxyethanol, cyclohexanol, 4-chlorobutanol and 2-phenylethanol.

One or more of the toxic alcohols (a) of the present invention can be incorporated into an active toxicant composition. The minimum concentration of alcohol in the composition required for the alcohol alone to provide an effective toxic amount varies considerably depending on the particular alcohol, the particular inert pharmaceutically acceptable carrier being employed and any other ingredients which are present. Thus, in one case a 10% concentration may suffice, while in other cases, concentrations as high as 30 to 40%

may be required to obtain an effective toxic dose.

In the following tables I and II, the results of pediculicidal and ovicidal testing, respectively, for various alcohols of this invention and other alcohols are set forth. The alcohols were tested in undiluted form (100% alcohol), as a 25% solution in water, and in a solution containing 15% of the alcohol, 25% isopropanol and 60% water ("15/25/60"). The results are set forth in terms of percent mortality.

Table I

		Pediculicidal Rating		
Alcohol	*Log P*	*100% Alcohol*	*25% Solution*	*15/25/60*
Methanol	-0.66	0	0	0
Ethanol	-0.32	45	0	0
iso-Propanol	-0.12*	65	0	0
n-Propanol	0.34	70	0	0
tert-Butanol	0.37	80	0	0
sec-Butanol	0.61	95	0	35
iso-Butanol	0.65	95	40	0
n-Butanol	0.88	100	20	0
Benzyl Alcohol	1.10	90	0	5
iso-Pentanol	1.16	100	55	80
2-Phenoxy-ethanol	1.16	100	5	5
Cyclohexanol	1.23	100	0	20
4-Chloro-butanol	1.27*	100	0	20
2-Phenyl-ethanol	1.36	100	0	80
n-Pentanol	1.40	100	10	75
n-Hexanol	2.03	100	5	85
n-Octanol	3.15	100	10	85
n-Decanol	4.15*	100	20	95
n-Dodecanol	5.13	100	10	100
Hexadecyl Alcohol	≤7.13*	100	40	90
Oleyl Alcohol	7.47*	100	0	40

Table II

Alcohol	*Log P*	*Ovicidal Rating* 100% Alcohol	*Ovicidal Rating* 25% Solution	*15/25/60*
Methanol	-0.66	4	27	0
Ethanol	-0.32	4	7	13
iso-Propanol	-0.12*	1	0	-
n-Propanol	0.34	27	23	-
tert-Butanol	0.37	16	17	0
sec-Butanol	0.61	10	46	32
iso-Butanol	0.65	0	58	2
N-Butanol	0.88	48	17	2
Benzyl Alcohol	1.10	100	100	29
iso-Pentanol	1.16	100	52	0
2-Phenoxyethanol	1.16	100	100	100
Cyclohexanol	1.23	100	0	57
4-Chlorobutanol	1.27*	100	100	100
2-Phenylethanol	1.36	100	100	34
n-Pentanol	1.40	100	67	35
n-Hexanol	2.03	100	100	100
n-Octanol	3.15	100	100	100
n-Decanol	4.15*	100	100	100
n-Dodecanol	5.13	100	100	100
Hexadecyl Alcohol	≤7.13*	100	75	29
Oleyl Alcohol	7.47*	84	0	20

The miticidal activity of the alcohols was determined, and the results are given in the Table III.

Table III

Alcohol	*log P*	*Miticidal Rating* 100%Alcohol	*Miticidal Rating* 50% Solution in Isopropanol
iso-Propanol	-0.12*	0	-
sec-Butanol	0.61	50	-
n-Butanol	0.88	100	-
Benzyl Alcohol	1.10	100	-
Cyclohexanol	1.23	-	100
2-Phenylethanol	1.36	100	-
n-Pentanol	1.40	100	-
n-Hexanol	2.03	100	-
Hexadecyl Alcohol	≤7.13*	-	100
Oleyl Alcohol	7.47*	30	-

Component (b) The toxicant component (b) of the instant invention can be certain ethoxylates i.e., certain derivatives of polyoxyethylene [$H(OCH_2CH_2)_nOH$]. The polyoxyethylene glycols *per se* have not been found to be pediculicidal or ovicidal. For convenience, polyoxyethylene will hereinafter be referred to as POE and the number of repeating units (n) will be indicated in parenthesis where applicable.

It has been found the the ethoxylates in themselves exhibit insecticidal and/or ovicidal activity, and their use as such forms the subject of our application No. 32134/77 (Serial No. 1604622). The same boundaries which delimit the insecticidal properties also include compositions which have a valuable degree of topical anesthetic performance. Although chemically unrelated to any of the conventional anesthetic configurations, these ethoxylates demonstrate topical pharmacologic properties which can be variously characterized as analgesic anesthetic or antiprurtic.

V.B. Wigglesworth (Journal of Experimental Biology, *21*, 3, 4 p. 97 (1945) in a study of transpiration through insect cuticles, reported on the moisture loss of *Rhodnius* nymphs following treatment with various surfactants. He observed that the ethoxylates of ring compounds had very little action, and that the eight mole ethoxylate of cetyl alcohol was the most effective surfactant be tested, the nymphs losing 48% of body weight in 24 hours. Wigglesworth failed to appreciate that this effect could be adapted to killing insects by an

action having no counterpart in higher animals.

Maxwell and Piper (Journal of Economic Entomology, *61*, No. 6, Dec. 1968 p. 1633) explored the lethal activity of a large series of ethoxylates against southern house mosquito pupae. They found activity at high dilutions (in the parts per million range), but contrary to Wigglesworth, they reported greatest activity with some ethoxylates of alkylphenols.

In tests against lice and their ova, we have made certain discoveries which were unexpected in light of Maxwell and Piper, and Wigglesworth. We found efficacy only at concentrations several orders of magnitude greater than Maxwell and Piper. Where they reported that short ethylene oxide chain lengths were less effective than 4-6 moles of ethylene oxide, we discovered that the aryl alkyl ethoxylates were best at 1-3 moles of ethylene oxide, and that such compounds were good ovicides but mediocre pediculicides. Certain ethoxylates of aliphatic alcohols were much superior both as insecticides and as ovicides. Moreover, those most effective as toxicants were also found to be most effective as topical anesthetics.

The ethoxylates of this invention are well known as surface active agents and have been incorporated in many pharmaceutical and cosmetic preparations as such. For example. polyoxyethylene (4) lauryl ether is 5.5% of a washable coal tar ointment, polyoxyethylene (23) lauryl ether is 8% of an all purpose anionic emulsion for skin application, and a mixture of these two lauryl ethers constitutes 35% of a commercial tar shampoo.

Smith (U.S. 2,666,728) teaches the use up to 5% of a nonionic polyethylene oxide ether of aromatic glycols in a composition for destroying lice. Lindner (U.S. 2,898,267) teaches the use of ethoxylates in emulsifiers for acaricidal compositions.

The POE derivatives which exhibit toxicant properties are the alkyl or aralkyl ethers, alkyl esters, and block polymers of polyoxyporpylene and/or ethylenediamine. Thus the alkyl or ester moiety, derived from a fatty alcohol or fatty acid respectively, contains 12 to 24 carbon atoms and preferably 12 to 20 carbon atoms. The alkyl moiety is preferably unsubstituted but can, if desired, contain an aryl substituent. The block polymers contain 6 to 100 POE units and 30 to 112 units of polyoxypropylene.

It has been observed that the POE alkyl ethers, alkyl esters and block polymers of polyoxypropylene and/or ethylendiamine require an appropriate hydrophilic-lipophilic balance (HLB) in order to contribute good activity. In general, the HLB can be 2.5 to 13.5. The alkyl ethers appear to contribute maximum activity at an HLB in the neighbourhood of 9, and the alkyl esters and block polymers at a lower HLB, excepting the alkyl diester, POE (8) dilaurate, having an HLB value of 10.

Exemplary of the POE alkyl ethers of the present invention are POE (1) lauryl ether, POE (2) oleyl ether, POE (2) stearyl ether, POE (3) oleyl ether, POE (3) tridecyl ether, POE (4) myristyl ether, POE (5) oleyl ether, POE (6) tridecyl ether and POE (10) oleyl ether. POE (1) ethylphenyl ether and POE (3) octylphenyl ether are examples of somewhat effective POE aryl alkyl ethers.

Typical examples of the POE esters include POE (3) oleate, POE (2) laurate and POE (8) dilaurate. Typical examples of the block polymers include Poloxamer 401 and Poloxamer 181. The minimum concentration of ethoxylate in the composition required for the ethoxylate alone to provide an effective toxic amount varies considerably depending on the particular ethoxylate, the particular inert pharmaceutically acceptable carrier being employed and any other ingredients which are present. Thus, in one case a 10% concentration may suffice, while in other cases, concentrations as high as 30 to 40% may be required to obtain an effective toxic dose.

In the following tables, the results of pediculicidal and ovicidal testing for various polyoxyethylene toxicants of this invention are set forth. The materials were tested in undiluted form (neat) or in a combination (C) containing 15% (w/w) compound, 25% isopropanol and 60% water. For comparative purposes, results achieved with the unmodified ethoxylate, i.e, polyethylene glycol (PEG, a Registered Trade Mark), and other ethoxylates not within the scope of this invention are also set forth.

Table IV. Pediculicidal and ovicidal activity for ethoxylate alcohols having a general structure type $H(OCH_2CH_2)_nOH$.

		% Mortality			
		Pediculicidal		Ovicidal	
Compound	*n*	*Neat*	*C*	*Neat*	*C*
diethylene glycol	2	0	5	0	54
PEG 12	12	25	35	35	16
PEG 32	32	(1)	20	0(2)	0
PEG 75	75	(1)	15	0(2)	14

Table V. Pediculicidal and ovicidal activity for a series of alkyl ethoxylate ethers.

		% Mortality			
		Pediculicidal		Ovicidal	
Compound	*HLB*	*Neat*	*C*	*Neat*	*C*
POE (1) lauryl ether	3.6	100	40	100(3)	100
POE (2) oleyl ether	4.9	100	10	100(3)	100
POE (2) stearyl ether	4.9	100	40	100	33
POE (3) oleyl ether	6.6	100	10	100	41
POE (3) tridecyl ether	8	100	20	100	100
POE (4) myristyl ether	8.8	100	35	100(3)	100
POE (5) olely ether	8.8	100	15	100	8.3
POE (4) lauryl ether	9.5	100	30	100	83
POE (6) tridecyl ether	11	100	30	100	0
POE (6.5) tridecyl ether	11.6	100	15	100	34
POE (6) lauryl thioether	11.6	100	20	100	0
POE (10) oleyl ether	12.4	100	10	5	68
POE (7) lauryl ether	12.5	100(4)	0	100(4)	36
POE (8) lauryl thioether	13.4	75	20	67	0
POE (9) lauryl ether	13.6	100	20	100(3)	19
POE (10) lauryl thioether	13.9	15	5	30	0
POE (12) lauryl ether	14.5	20	5	100	0
POE (20) isohexadecyl ether	15.7	(1)	0	11(2)	2
POE (23) lauryl ether	16.9	(1)	0	69(2)	3

Table VI. Pediculicidal and ovicidal activity for some arylalkyl ethoxylate ethers.

		% Mortality			
		Pediuclicidal		*Ovicidal*	
Compound	*HLB*	*Neat*	*C*	*Neat*	*C*
POE (1) octylphenyl ether	3.6	80	10	100(3)	66
POE (3) octylphenyl ether	7.8	15	5	82(3)	34
POE (10) nonylphenyl ether	13.4	20	5	82(3)	0

Table VII. Pediculicidal and ovicidal activity for ethoxylate mono and diesters.

		% Mortality			
		Pediculicidal		*Ovicidal*	
Compound	*HLB*	*Neat*	*C*	*Neat*	*C*
POE (2) oleate	3.5	70	75	100(3)	14
POE (2) laurate	6.0	25	20	100(3)	6.5
POE (8) dioleate	7.2	40	0	7.3	28
POE (2) laurate	7.4	95	55	100(3)	8.3
POE (8) distearate	7.8	(1)	40	(1)	23
POE (4) laurate	8.6	10	15	14	5.9
POE (4) sorbiton septaoleate	9	5	20	77	21
POE (8) dilaurate	10	80	10	23	38
POE (12) distearate	10.6	(1)	40	(1)	24
POE (20) stearate	15	(1)	0	(1)	0
POE (100) stearate	18.8	(1)	0	(1)	5

Table VIII. Pediculicidal and ovicidal activity for ethoxylate block polymers having the general structure type outlined for each section.

A) based on structure type

$$HO(\underset{\substack{|\\CH_3}}{CH}CH_2O)_x(CH_2CH_2O)_y(\underset{\substack{|\\CH_3}}{CH}CH_2O)_zH$$

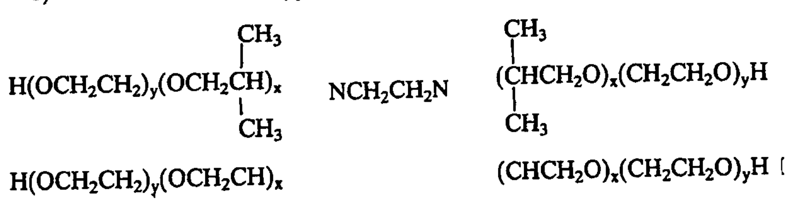
				% Mortality			
				Pediculicidal		*Ovicidal*	
x	*y*	*z*	*HLB*	*Neat*	*C*	*Neat*	*C*
18	14	18	4.5	10	0	56	4.8
12	23	12	8.4	5	0	0	15
7	22	7	10.8	10	0	0	41

B) based on structure type

$$HO(CH_2CH_2O)_x(\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2O)_y(CH_2CH_2O)_zH$$

				% Mortality			
				Pediculicidal		Ovicidal	
x	*y*	*z*	*HLB*	*Neat*	*C*	*Neat*	*C*
3	30	3	3	10	0	70	0
13	67	13	4	-	10	0(2)	1.2
6	67	6	5	55	0	80	84
8	30	8	7	0	50	8.4	0
21	67	21	8	(1)	10	0(2)	4.5
13	30	13	15	5	20	0	17
38	54	38	15	(1)	0	0(2)	19
122	47	122	27.5	(1)	40	(1)	4.5

C) based on structure type



			% Mortality			
			Pediculicidal		Ovicidal	
x	*y*	*HLB*	*Neat*	*C*	*Neat*	*C*
18	*2*	*2*	*5*	*20*	*79*	*0*
12	2	3	45	0	73(3)	11
21	7	3.5	30	0	100(3)	53
26	8	5	5	0	100(3)	49
13	4	7	0	20	58	0
26	24	13	85	0	-	20
8	7	16	0	20	0	28

Notes to Tables IV-VIII
(1) solid - could not be tested at 100%
(2) 50% (w/w) in ethanol
(3) pad noted to be coated with compound at conclusion of test
(4) 90% (w/w) in water

The pediculicidal activity of various compounds se forth in Table V as a function of concentration was determined in a diluted system containing 25% isopropanol and water q.s. The results are shown in Table IX.

Table IX

	Concentration, %(w/w)		*Mortality, %*
A. POE (1)	*lauryl ether*	*HLB* = 3.6	
	10		55
	15		40
	20		80
	30		85
	40		80
	50		95
B. POE (2)	oleyl ether	HLB = 4.9	
	10		30
	15		10
	20		35
	30		15
	40		20
	50		35
C. POE (2)	stearyl ether	HLB = 4.9	
	10		0
	15		40
	20		80
	30		50
	40		100
	50		100
D. POE (3)	oleyl ether	HLB = 6.6	
	15		10
	20		15
	30		60
	40		70
	50		100
	60		100
E. POE (3)	tridecyl ether	HLB = 8	
	10		25
	15		20
	20		95
	30		95
	40		100
	50		100
F. POE (4)	myristyl ether	HLB = 8	
	10		75
	15		35
	20		90
	30		100
	40		100
	50		100
G. POE (4)	lauryl ether	HLB = 9.5	
	10		15
	15		30
	20		55
	30		80
	40		85
	50		60

H. POE (6)	tridecyl ether	HLB = 11	
	10		40
	15		30
	20		65
	30		75
	40		35
	50		55
I. POE (6.5)	tridecyl ether	HLB = 11.6	
	15		15
	20		25
	30		5
	40		35
	50		30
	60		60
J. POE (7)	lauryl ether	HLB = 12.5	
	15		0
	20		10
	30		20
	40		20
	50		35
	60		40
K. POE (9)	lauryl ether	HLB = 13.6	
	15		20
	20		25
	30		15
	40		25
	50		70
	60		50
L. POE (12)	lauryl ether	HLB = 14.5	
	15		5
	40		0
	50		15
	60		30
	70		45
M. POE (23)	lauryl ether	HLB = 16.9	
	15		0
	20		0
	30		0
	40		0
	50		0
	60		5

The pediculicidal activity of two ethoxylated alkyl ethers as a function of concentration when diluted with water was determined and the results are set forth in Table X.

Table X

	Concentration, % (w/w)		*Mortality, %*
A. POE (2)	oleyl ether	HLB = 4.9	
	5		0
	10		10
	20		35
	30		90
	40		100
	60		100
	80		100
	100		100

	Concentration, % (w/w)		% Mortality
B. POE (4)	lauryl ether	HLB = 9.5	
	5		5
	10		5
	15		45
	20		100
	80		100
	90		100
	100		100

The ovicidal activity of various compounds set forth in Table V as a function of concentration was determined in a diluted system containing 25% isopropanol and water q.s. The results are shown in Table XI.

Table XI

	Concentration, % (w/w)		*% Mortality*
A. POE (1)	lauryl ether	HLB = 3.6	
	1		100
	3		100
	5		100
	7		100
	9		100
B. POE (3)	tridecyl ether	HLB = 8	
	10		100
	15		100
	20		100
	30		100
	40		100
C. POE (4)	myristyl ether	HLB = 8.8	
	10		27
	15		100
	20		100
	30		92
	40		100
	50		100
D. POE (6)	tridecyl ether	HLB = 11	
	10		0
	15		0
	20		16
	30		44
	40		14
	50		3
E. POE (12)	lauryl ether	HLB = 14.5	
	15		0
	30		0
	40		0.2
	50		5
	60		2
	70		0
F. POE (23)	lauryl ether	HLB = 16.9	
	15		3
	20		10
	30		4
	40		5
	50		0
	60		5

Table XII reflects the resulting pediculicidal and ovicidal activity of a 15% (w/w) concentration of POE (4) lauryl ether with variation of isopropanol and water content.

Table XII

% w/w isopropanol	% w/w water	% Mortality Pediculicidal	Ovicidal
25	60	30	83
20	65	30	21
15	70	15	19
10	75	15	15
5	80	95	100
1	84	20	100
0	85	45	10

As can be seen from Table XII, the 15% concentration of POE (4) lauryl ether exhibited synergistic pediculicidal activity when the isopropanol was 1-5%.

The most effective polyoxyethylene toxicants of this invention have also been found to exhibit topical anesthetic activity. Thus, for example, one drop of 5% aqueous POE (4) lauryl ether caused an onset of corneal anesthetic action in 5-8 minutes with a duration of 0.5-4 hours (average for four tests was two hours) in a modified Cole and Rose rabbit eye irritation test (J. Lab & Clin. Med. 15:239, 1929). In contrast, POE (23) lauryl ether did not exhibit any activity in the same test. In general, the preferred alkyl ethers exhibit anesthetic, analgesic or antipruritic activity at concentrations of at least 1% and are preferably employed for this purpose at 1-10%.

The miticidal activity of some of the instant toxicants was determined.

Table XIII shows the miticidal activity of a 50% (w/w) concentration of the named compounds in isopropanol.

Table XIII

Compound	*HLB*	*Miticidal Activity, %*
POE (1) lauryl ether	3.6	100
POE (2) oleyl ether	4.9	80
POE (4) myristyl ether	8.8	100
POE (4) lauryl ether	9.5	100
POE (6) tridecyl ether	11	90
POE (10) oleyl ether	12.4	100
POE (12) lauryl ether	14.5	100

Component (c) The toxicant component (c) of the instant invention are those N-substituted -β-aminopropionic acids in which the N-substitutent is derived from a fatty material. Thus, the N-substituted group is preferably an alkyl group which can contain 8 to 24 carbon atoms, preferably 10 to 18 carbon atoms and most preferably about 12 carbon atoms. N-coco-β-aminopropionic acid and N-lauryl-myristyl-β-aminopropionic acid are typical examples of the toxicants (c) of this invention.

The toxicants (c) are amphoteric surfactant materials and have been used heretofore in certain shampoo and other "cosmetic" formulations as foaming, cleansing and conditioning agents usually at a concentration of 10% or less. For example, a "cosmetic" type of liquid shampoo containing 10% of the sodium salt of N-Coco-β-aminopropionic acid, 8.25% triethanolamine lauryl sulphate, 2.5% of coconut diethanolamide, sufficient lactic acid to adjust the pH to 4.5-5.0, perfume colour and water q.s. ad. 100% is known. This shampoo is not known to be an ectoparasiticide. Indeed, in the known formulations, the aminopropionic acids are not generally pediculicidal or ovicidal. The discovery that such components possess ectoparasiticidal activity is the subject of our application 32140/77 (Serial No. 1604858).

The aminopropionic acids of this invention, especially the N-alkyl aminopropionic acids, can be employed as free acids or in equilibrium with their salts. In order that the acids contribute the desired activity, it is necessary that the formulation in which they are used have a pH on the acid side, that is, less than 7.0, preferably 6.8 or less. It is preferred to maintain the pH at about 3.0 or above and it has been observed that maximum activity occurs at a pH value in the neighbourhood of 4. The pH of the formulation in which the aminopropionic acid is used can be adjusted by any known and convenient means such as, for example, by the use of an appropriate acid, ion exchange resin, etc. It is also necessary that shampoo formulations in which the aminopropionic acids are used do not contain a strong detergent. For example, the known cosmetic shampoo formulation referred to

earlier does not contain an effective toxic amount of the aminopropionic acid, as defined herein, because of the presence of the triethanolamine lauryl sulfate. The lauryl sulfate tends to remove the active residue which would otherwise continue to act on the lice or their ova.

One or more of the toxic aminopropionic acids (c) of the present invention can be incorporated into an active toxicant composition. The minimum concentration of aminopropionic acid in the composition required for the acid alone to provide an effective toxic amount varies considerably depending on the particular aminopropionic acids, the particular inert pharmaceutically acceptable carrier being employed and any other ingredients which are present. Thus, in one case a 10% concentration may suffice, while in other cases, concentrations as high as 25% may be required to obtain an effective toxic dose. Usually, the aminopropionic acids will be used in concentrations of 0 to 25% and most preferably at concentrations of 10 to 20%.

In Table XIV, the results of pediculicidal and ovicidal testing for toxicants of this invention are set forth. For comparative purposes, results achieved with the acids at a basic or substantially neutral pH (in the form of the sodium or triethanolamine salt) are also set forth. The compounds were tested in the form of 20 weight percent solution in water at the indicated pH.

Table XIV

Compound	*pH*	*Mortality, %* *Pediculicidal*	*Ovicidal*
N-Coco-β-aminopropionic acid	4	100	100
N-Coco-β-amino-propionic acid	6.2	100	28
N-Coco-β-amino propionic acid sodium salt	12.5	5	20
N-Lauryl-myristyl-β-aminopropionic acid	4	100	100
N-Lauryl-myristyl-β-amino-propionic acid	5.3	100	10
N-Lauryl-myristyl-β-aminopropionic acid triethanolamine salt	7.5	15	0

The pediculicidal activity of two toxicants of this invention as a function of concentration was determined. Table XV sets forth the results employing solutions of N-coco-β-aminopropionic acid in water and Table XVI sets forth the results using N-lauryl-myristyl-β-aminopropionic acid in water.

Table XV

Pediculicidal activity of N-Coco-β-Aminopropionic acid as a function of concentration.

Concentration, % by Weight	*Mortality, %*
5	40
10	95
20	100
30	100
40	100

Table XVI

Pediculicidal activity of N-Lauryl-Myristyl-β-amino-propionic acid as a function of concentration

Concentration, % by weight	*Mortality, %*
5	45
10	95
20	100
30	100
40	100

Component (d) The toxicant component (d) of the instant invention are those N-acyl-N-methyl glycines in which the acyl moiety contains 12 to 20 carbon atoms, preferably 13 to 20 carbon atoms. Typical examples of the glycines are lauroyl sarcosine (N-lauroyl-N-methyl glycine), oleoyl sarcosine (N-oeloyl-N-methyl glycine) and cocoyl sarcosine (N-cocyl-N-methyl glycine).

These N-acyl sarcosines, i.e, N-acyl-N-methyl glycines, can contribute effective ovicidal activity, often with a useful degree of insecticidal activity. These glycines are well known as surface active agents and have been incorporated in many pharmaceutical and cosmetic preparations as such. For example, tetradecylamine lauroyl sarcosinate has been used in an anti-dandruff preparation and cocoyl sarcosine constitutes greater than 10% of "Head and Shoulders" shampoo. Cocoyl sarcosine has been used in hair tint shampoos at a pH of 5.5. It is also of interest that Dvorokovitz (U.S. 2,890,960) teaches the use of antienzymes including lauryl sarconsinic acid to retard ovi-deposition in fruit flies.

Conventional shampoo formulations generally have pHs in excess of 5.5. It has been observed that only the acid form of the sarcosine is active and therefore the pH of a formulation containing the sarcosine must be less than 5.5 for the material to exhibit optimum pediculicidal and ovicidal activity. Accordingly, the prior art shampoos employed the sarcosine as a surfactant in the form in which they were not toxicant, except to the limited extent that the acidic form may have existed in equilibrium with the ionized salt. The discovery of insecticidal activity in these compounds is the subject of our application 32136/77 (Serial No. 1604854).

One or more of the toxic glycines of the present invention can be incorporated into an active toxicant composition. The minimum concentration of glycines in the composition required for the glycine alone to provide an effective toxic amount varies considerably depending on the particular glycine, the particular inert pharmaceutically acceptable carrier being employed and any other ingredients which are present. Thus, in one case a 5% concentration may suffice, while in other case, concentrations as high as 30 to 40% may be required to obtain an effective toxic dose. In most instances, however, a concentration of 1 to 15% is sufficient. Higher concentrations may be irritating to the skin or eyes of vertebrates.

The formulation in which the glycine is used should have a pH below about 5.5. It is preferred to maintain the pH above about 2.0 and the preferred pH range is about 3 to 5. As with component (c), the pH can be adjusted by procedures well known in the art, e.g. by using a suitable acid, ion exchange resins, etc.

In the following tables XVII and XVIII, the results of pediculicidal and ovicidal testing of lauroyl sarcosine is set forth. The sarcosine was tested at various concentrations in a formulation which contained 25% isopropanol and water q.s. ad. 100%.

Table XVII — Pediculicidal Activity

	Concentration, %	Mortality, %
Acid		
	1	0
	2	5
	3	5
	4	5
	5	20
	6	75
	7	90
	8	100
Sodium Salt		
	30	5
	40	0
	50	5
	60	5
	70	5
	80*	0
	90*	0

*isopropanol level was zero in these samples.

Table XVIII — Ovicidal Activity

	Concentration, %	Mortality, %
Acid		
	1	82
	2	62
	3	96
	4	100
	5	100
	6	100
	7	100
	8	100
	9	100
	10	100
Sodium Salt		
	30	0
	40	20
	50	12
	60	38
	70	0
	80*	34
	90*	77

*isopropanol level was zero in these samples.

Tables XVII and XVIII illustrate that when the sarcosine is used in the form of sodium salt, i.e., at an approximately neutral pH, the formulations are not strongly pediculicidal or ovicidal.

The pediculicidal and ovicidal activity of oleoyl sarcosine as a function of concentration was determined in a formulation which contained 25% isopropanol and water q.s. ad 100%. The results are shown in table XIX.,

Table XIX

Concentration, %	Mortality, % Pediculicidal	Ovicidal
1	40	77
2	75	100
3	75	100
4	55	100
5	65	100
6	100	100
7	95	100
8	100	100

The pediculicidal and ovicidal activity of cocoyl sarcosine was determined as a function of concentration in a system containing 25% isopropanol and water q.s. ad. 100%. The results are shown in Table XX.

Table XX

Concentration, %	Mortality, % Pediculicidal	Ovicidal
1	5	100
2	5	93
3	15	100
4	10	100
5	35	100
6	50	100
7	40	100
8	40	100
9	75	100
10	80	100
12	70	-
15	100	-

The sarcosines may be used in formulations other than those used to determine the data set forth in the foregoing tables. For example, a composition containing 50% stearoyl sarcosine and 50% ethanol has an activity of 80% in the standard ovicidal testing described before. Similarly, a formulation containing 15% stearoyl sarcoside, 25% isopropanol, 7% Tween (Registered Trade Mark) 80 and 53% water exhibits 100% activity in both the pediculicidal and ovicidal tests hereinbefore described.

It will be apparent from the foregoing detailed description of the components (a) to (d) that in themselves they can each contribute toxicant activity to a composition of the present invention. If desired, other toxicants may be employed in addition to (a) with (b), optionally with (c) and/or (d). Conventional additives may be employed with the carrier in order to facilitate preparation of the desired form of composition or improve the properties of the resultant composition. Given the above description the skilled man will readily be able to formulate a composition using the present toxicants in otherwise conventional forms of composition, and moreover will have no difficulty in finding other examples of the components (a) to (d) which can be used. In certain instances some synergism may be found upon testing the compositions of the invention.

The present invention will now be illustrated by the following selection of examples. Each example gives a formulation which is made up in to the stated form (e.g. gel, cream, etc) using conventional techniques.

Example 1

Gel		
	n-Octanol	31
	POE (2) Stearyl ether	10
	oleoyl sarcosine	8
	xanthan gum	3
	water and acetic acid to pH 5	48

Example 2

Cream

cetyl alcohol	13.0
cocoyl sarcosine	14.0
glyceryl monostearate	8.0
sorbitan monostearate	8.0
POE (1) ethylphenyl ether	10.0
isopropanol	15.0
xanthan gum	0.3
water	42.7

Example 3

Clear shampoo

n-butanol	25
poloxamer 401	17
N-lauryl-myrsityl-β-amino-propionic acid	10
triethanolamine lauryl sulfate	8
water and hydrochloric acid to pH 4.0	40

Example 4

Aerosol Spray

isopropanol	36
n-hexanol	10
N-coco-β-aminopropionic acid	20
POE (4) myristyl ether	1
water and hydrochloric acid to pH 4.0	19
isobutane	15

Example 5

Cream

isopentanol	25.0
POE (2) oleyl ether	10.0
glyceryl monostearate	22.5
sorbitan monostearate	1.4
polysorbate 60	3.4
xanthan gum	0.4
water	32.3

Example 6

Quick Breaking Aerosol Foam

POE (4) lauryl ether	8
n-octanol	15
isopropanol	25
glycerine	3
isobutane	8
water	41

Example 7

Powder

4-chlorobutanol	7
POE (3) tridecyl ether	3
talc	90

Example 8

Clear colourless liquid suitable for mechanical spray application or inunction

isopropyl alcohol	55
hexadecyl alcohol	15
POE (8) dilaurate	10
water	20

Example 9

Clear shampoo

isopropyl alcohol	22
POE (4) lauryl ether	23
POE (23) lauryl ether	7
n-dodecanol	12.8
benzalkonium chloride	0.2
water	35

Example 10

Lotion

isopropyl alcohol	25
hexadecyl alcohol	15
carboxypolymethylene	0.1
N-coco-β-aminopropionic acid	1.0
water and hydrochloric acid to pH 4	58.9

Example 11

Gel

carboxypolymethylene	1.5
isopropyl alcohol	23.0
4-chlorobutanol	12.0
polysorbate 80	4.0
triethanolamine	3.0
POE (2) oleyl ether	10.0
water	46.5

Example 12

Lotion

ethanol	45.0
sodium carboxymethyl-cellulose	0.3
carbopol 941	0.3
hexadecyl alcohol	20.0
triethanolamine	0.3
acetylated polyoxyethylated (10) lanolin	3.1
water	31.0

Example 13

Lotion

polyoxyethylene (10) cetyl ether	3.0
talc	1.5
carbopol 941	0.3
triethanolamine	0.3
ethyl alcohol	40.0
dodecanol	15.0
water	39.0

Example 14

Aerosol Spray

cyclohexanol	48
isopropanol	25
POE (4) lauryl ether	2
water	8
isobutane	17

Example 15

Cream

cetyl alcohol	13.0
n-decanol	7.0
glyceryl and sorbitan monostearates	22.0
POE (8) dilaurate	4.7
xanthan gum	0.3
water	53.0

Various changes and modifications can be made: the various embodiments disclosed herein are for the purpose of further illustrating the invention but are not intended as limiting. In the specifications of our said applications 32134/77, 32136/77, 32139/77 and 32140/77 (Serial No. 1604622 1604854 1604857 and 1604858) we give examples for formulations containing individual ones of the components (a) to (d), and such formulations can readily be modified to be in accordance with the present invention. Equally the skilled man will have no difficulty in formulating *ab initio*. Throughout this specification including the claims, all temperatures are in degrees Centigrade and all parts and percentages are by weight unless otherwise indicated.

WHAT WE CLAIM IS:

1. A method of controlling ectoparasites or their ova which comprises applying to a substrate a mixture of:

(a) a monohydric alcohol whose logarithm of the partition coefficient between N-octanol and water (log P) is at least 0.61; and

(b) a polyoxyethylene derivative having an HLB of 2.5 to 13.5 and being an alkyl ether, aralkyl ether, alkyl ester or block polymer of polyoxyethylene.

2. A method according to Claim 1 wherein the mixture further contains:

(c) an N-fatty-β-aminopropionic acid.

3. A method according to Claim 1 or Claim 2 wherein the mixture further contains:

(d) an N-C_{12-24}acyl-N-methyl glycine.

4. A method according to any one preceding claim wherein the substrate is human.

5. An active toxicant composition comprising a mixture of (a) and (b) as defined in Claim 1 together with a pharmaceutically acceptable carrier.

6. A composition according to Claim 5 which additionally comprises (c) and/or (d) as defined in Claims 2 and 3 respectively.

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